REMARKS

The Office Action, dated December 21, 1999, has been carefully considered. The claims have been amended to more clearly set forth the Applicants' contribution to the art and do not introduce new matter into the disclosure of the invention. The basis for the amendments to the claims can be found on pages 10-21 and further on pages 28-31 of the Specification. It is believed that no additional fee is required as the number of independent and dependent claims is the same as originally filed.

Rejections under 35 U.S.C. 112, First Paragraph

The Examiner has rejected claim 1, under 35 U.S.C. 112, first paragraph, contending that this claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Specifically, the Examiner contends that there is no literal support for the limitation in Claim 1 that recites "injecting the human or animal with an amount of neutralizing targeting moiety, capable of binding specifically to the target analyte, at a concentration in excess of measurable quantities of secreted analyte."

As discussed in the telephonic interview, the amount of neutralizing targeting moiety must inherently be in excess of the circulating levels of analyte in the target host in

order to sufficiently bind the analyte present and to be able to measure analyte secreted by the host. Claim 1 has now been amended to further clarify the amounts required.

Because only the complex of analyte and labeled analyte-binding molecule would be detected in the in vitro assay, a sufficient quantity of labeled analyte-binding molecule must be injected into an animal to assure that the measurable fraction of the secreted analyte would bind and remain bound to a labeled analyte-binding molecule. Antecedent basis can be found on page 19, lines 5, 6, 11 and 12, and page 21, lines 7-13.

Rejections under 35 U.S.C. 112, Second Paragraph

The Examiner has rejected claims 1-42, as amended, under 35 U.S.C. 112, second paragraph, contending that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as the invention. The claims have now been amended herein to address the issues raised by the Examiner and the Examiner's Supervisor in the earlier telephonic interview.

Specifically, the Examiner contends that claim 1, step e, lacks literal antecedent basis in reciting "the assay mixture of step d". Step e has been amended to recite "in order to form an assay mixture" for proper antecedent basis. In addition, the phrase "the analyte determinants of" has been deleted to make it clear that the capture moiety binds specifically to the conjugate.

The Examiner contends that claim 1, step f, is indefinite in reciting "removing any unbound targeting moiety from the capture moiety". The claim has been amended to recite "removing any unbound and unconjugated targeting moiety and target analyte from the assay mixture" in order to make the claim definite.

The Examiner contends that claim 1, step g, is indefinite in providing detection labels without setting forth any steps involved in the process. The claim has been amended to recite "the amount of bound targeting moiety:target analyte conjugate" in order to make the claim definite.

The Examiner contends that claim 1, step h, is incomplete for omitting essential structural cooperative relationships of the elements "detection step" in step (g) and the "determination step" in step (h). The claim has been amended to recite "correlating to the bound targeting moiety:target analyte conjugate detected in step (g)" in order to make the claim complete.

The Examiner has rejected claim 1, under 35 U.S.C. 112, second paragraph, contending that claim 1 is incomplete for omitting an essential step of detection of the target analyte using detection labels. Therefore, step g has been amended to read "detecting bound targeting moiety: target analyte conjugate on the capture moiety using one or more detection labels".

The Examiner contends that claim 12 is indefinite for reciting a use without any active, positive steps delimiting how this is actually practiced. Claim 12 has been amended to recite "wherein the label is selected from the group consisting of" to clarify this claim.

The Examiner contends that claims 24 is of improper dependent form for failing to further limit the subject matter of the previous claim to which it depends upon. Claim 24 has been cancelled to correct this matter.

The Examiner contends that claim 34 is indefinite and inconsistent with claim 1 in reciting the phrase "containing a labeled targeting moiety specific for the target analyte" whereas claim 1 does not recite a labeled targeting moiety. Claim 34 has now been amended to depend from claim 12.

The Examiner contends that claim 34 is indeterminate in scope by reciting "targeting moiety specific for the target analyte" and "contains the standard for the analyte" since the claim does not specifically identify the metes and bounds of the "target analyte". Step (c) of claim 34 was amended in the previous amendment filed October 7, 1999, to recite "contains the standard for the target analyte."

Based on the foregoing amendments and remarks, it is submitted that the 35 U.S.C. 112 rejections have been overcome and it is respectfully requested that they be withdrawn.

Rejection under 35 U.S.C. 103

Examiner has rejected claims 1-42, under 35 U.S.C. 103(a), as being unpatentable over Tamarkin *et al.* (US 5,328,899), in view of Finkelman *et al.* (Journal of Immunology 151:1235-1244 (1993)) and in further view of Pouletty *et al.* (US 5,612,034). Examiner has further rejected claims 1-42, under 35 U.S.C. 103(a), as being unpatentable over Tamarkin *et al.* (US 5,328,899), in view of David *et al.* (US 4,486,530) and Gosling (Clin. Chem. 36(8): 1408-1427 (1990)), in further view of Finkelman *et al.* (Journal of Immunology 151:1235-1244 (1993)) and in further view of Pouletty *et al.* (US 5,612,034). Applicants maintain the arguments of record and respectively traverse this rejection.

The present invention, as defined by amended claim 1, relates to a method for measuring the endogenous levels of a secreted analyte, such as a cytokine. The present invention provides the capability of measuring basal, as well as stimulated, cytokine production. The cited references do not provide the necessary specific motivation, much less a reasonable expectation of success in solving the issues of the present invention.

Applicants submit herewith a declaration from Ethan M. Shevach, M.D., demonstrating that one of ordinary skill in the field of immunology and medical science would not deduce the present invention upon reading the references cited by the Examiner, either alone or in combination.

The assay disclosed by Tamarkin reference is different than the present invention. The Tamarkin assay is a competitive binding assay where polyclonal antibodies are adhered to a plate. The assay measures the ability of an analyte present in a serum sample to block the binding of biotin-labeled analyte to the plate. In such an assay, if the bodily fluid contains a large amount of analyte, most or all antibody adhered to the plate is bound by the analyte so that the biotin-labeled analyte is unable to bind to free antibody. As the amount of analyte present in the biological fluid increases, the biotin-labeled cytokine binding decreases.

The Tamarkin reference teaches using a single, polyclonal antibody, not two specific binding molecules (preferably monoclonal antibodies); it is not utilized in vivo to obtain the specific amount of analyte excreted over a fixed period of time; it does not teach using an excess of binding molecule; and it does not teach using a neutralizing binding molecule that binds the analyte and prevents its catabolism, excretion, or binding to its respective receptor.

David *et al.* teaches only that a two-site or sandwich type assay may be used to determine the presence and concentration of an antigen. There is no mention or suggestion that such an assay may be used to determine analyte production *in vivo*.

While Gosling *et al.* is a generalized reference that discloses the use of an excess of

antibody to eliminate differences in affinity, there is no mention or suggestion that such an assay may be used to determine analyte production *in vivo*. Gosling does not teach, suggest, or even mention using a neutralizing binding molecule that binds the analyte and prevents its catabolism, excretion, or binding to its respective receptor at all.

Accordingly, lacking a technological rationale, the reasonable expectation of success, and motivation, it is not seen how any combination of the cited references could establish a prima facie case of obviousness.

In summary, the skilled artisan would find nothing in Tamarkin, Finkelman, Pouletty, David, or Gosling alone or in combination that would teach or suggest the present invention or any reason for making it. Furthermore, there is no motivation to combine the references in such a way as to get to the claimed invention. Therefore, the present invention is not obvious under 35 U.S.C. Sec. 103 and, accordingly, an obviousness rejection under this section is improper and the Applicants request reconsideration and withdrawal of this rejection.

In view of the above, it is respectfully submitted that the claims as amended and presently before the Examiner are in condition for allowance. Accordingly, reconsideration and withdrawal of the rejections and objections are requested and allowance of claims 1 through 42 is solicited.

Respectfully submitted,

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